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Marianne L. Horinko, Acting Administrator
US Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: Comments on the HPV test plan for 2,3,4,5,6-pentachloropyridine

Dear Acting Administrator Horinko,

The following are comments on the HPV test plan for 2,3,4,5,6-pentachloropyridine (pentachloropyridine; CAS no. 2176-62-7), submitted by Dow Chemical Co. (Dow). These comments are submitted on behalf of the Physicians Committee for Responsible Medicine, People for the Ethical Treatment of Animals, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These animal, health and environmental protection organizations have a combined membership of more than ten million Americans.

Dow proposes to conduct a developmental toxicity test using rats, but does not state the exact test to be used, i.e., the OECD number. Dow refers to the test only as a "teratology study" (test plan, pp. 2, 4). Also, it is not clear what Dow means by its plan to conduct both a "probe study" and a full study (p. 4). We very much hope Dow does not intend to conduct animal studies that even EPA does not require under the HPV program. These issues require clarification.

Dow also intends to conduct an *in vitro* rat lymphocyte cytogenetics assay, again without specifying the OECD protocol number. While this is called an *in vitro* assay, animals are still used and it will result in the death of 40 rats. As noted below, there are *in vitro* cytotoxicity data available in the published literature, which should address this SIDS testing endpoint (Nehez, et. al., 1993)

Although Dow implies that no information is available about the developmental toxicity of pentachloropyridine (summaries, section 5.9), we have found that at least one study has in fact been conducted. In this study, oral doses (100 mg/kg/day) of pentachloropyridine on gestation days 6 – 15 were found to cause no embryotoxicity or fetal malformations in Halle:DBA or Halle:AB mice (Nehez, et. al., 1993). In addition, in a separate study (also in Nehez, et. al., 1993), bone marrow chromosome analyses at 24 and 48 hours after a single oral dose of 11.75 mg/kg pentachloropyridine in male mice (CFLP) was negative for mutagenic activity. These studies should be included in Dow's test plan and the data used to reduce or eliminate the proposed tests, saving more than 1300 animals. It is imperative that ALL available data be utilized to eliminate any new tests using animals.

If, nevertheless, Dow judges that further developmental toxicity data are needed, the existing developmental/embryotoxicity study by Nehez et. al. (1993) could be used in conjunction with an *in vitro* test: the rodent embryonic stem cell test. This test has recently become commercially available in the US, and last year it was validated by the European Centre for the Validation of Alternative Methods, after which the Centre's Scientific Advisory Committee concluded that it was ready to be considered for regulatory purposes (Genschow 2002). We hope that Dow will contact us for advice about the laboratories that are currently conducting this test. This would provide Dow with an opportunity to work with EPA and the animal welfare community to promote this *in vitro* test as a means of addressing relevant HPV/SIDS endpoints.

Lastly, and at the very least, Dow needs to clarify which specific "teratology" protocol they plan to pursue. If Dow intends to follow OECD No. 414, this will kill at least 1,300 animals. However, there is no need for Dow to carry out OECD no. 414, as OECD no. 422, a combined repeat-dose, developmental and reproductive toxicity test method, has been approved by the EPA for developmental toxicity data in the HPV program. OECD no. 422 will kill approximately 700 animals.

Thank you for your attention to these comments. I can be reached at 202-686-2210, ext. 302 or by email at csandusky@pcrm.org.

Sincerely,

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Director of Research

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References

Genschow, E., *et al.*, "The ECVAM international validation study on *in vitro* embryotoxicity tests: Results of the definitive phase and evaluation of prediction models", *Alternatives to Laboratory Animals* 30: 151-76, 2002.

Nehez, M., *et al.*, "Investigations on the cytogenetics and embryotoxic activity of pentachloropyridine", *International Journal of Environmental Health Research* 3: 171-176, 1993.

NIOSH, National Occupational Exposure Survey (1981-1983), http://www.cdc.gov/noes/noes1/x4381sic.html.